PATENT SPECIFICATION 1,197,809

DRAWINGS ATTACHED.

Date of Application (No. 32179/68) and filing Complete Specification: 5 July, 1968.

Application made in Japan (No. 9011) on 13 Feb., 1968.

Complete Specification Published: 8 July, 1970.

1,197,809

Index at acceptance:—B1 GX; C2 C(2D19, 3A7V4A1, 3A7V4F1, 3A7V4F2, 3A7V4H, 20Y, 213, 215, 22Y, 220, 227, 246, 247, 25Y, 250, 251, 29Y, 29X, 30Y, 302, 31Y, 313, 32Y, 321, 332, 339, 34Y, 342, 351, 352, 36Y, 360, 361, 362, 366, 367, 571, 581, 591, 601, 62X, 620, 623, 628, 638, 652, 658, 670, 761,

PATENTS ACT 1949

SPECIFICATION NO. 1,197,809

The following corrections were allowed under Section 76 on 19 March 1971

Page 7, line 91, *for* '2.16%' *read* '2.18%'

THE PATENT OFFICE
7 May 1971

R 2188/5

which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method for continuous optical resolution of a solution of an organic racemate into crystals of desired optical isomer.

Various methods for optical resolution of organic racemates have been heretofore proposed. Methods based on fractional crystallization using a physico-chemical means have been regarded as more advantageous than chemical or biological methods, for the former methods require no expensive reagent for resolution and can be carried out economically on an industrial scale.

A number of methods for optical resolution of organic racemates using physico-chemical resolution have been patented, but these methods have been all based merely on experiments and not on a theory or generalization derived from the experiments. Thus:

(1) The relation between the applicability of resolution methods based on the fractional crystallization and the constitution of organic racemates is not clearly predictable and must apparently be checked experimentally case by case [Chem. Rev. *3*, 297 (1963)].

(2) A basis for controlling the optical resolution utilizing fractional crystallization is not clearly predictable. When the degree of supersaturation of organic racemate is high, however, such limit is not clearly predictable because the basis of such a limit has not been elucidated. Therefore, such a limit for an individual organic racemate must apparently be experimentally determined case by case.

(3) A large number of resolution means for various organic substances based on fractional crystallization have been proposed. However, what type of means is to be employed depends entirely upon experiment for the case concerned because the resolution is greatly influenced by the physical properties of the organic racemate to be resolved. The heretofore proposed means are as follows:

A. Utilization of supersaturation:
   (a) A means based on the preparation of a supersaturated solution of the organic racemate in advance and successive seeding of crystals of the desired optical isomer.
   (b) A means based on the supersaturation of an organic racemate solution after seeding.

B. Utilization of seeding:
   (a) A means based on seeding crystals of the desired optical isomer.
   (b) A means based on the simultaneous seeding of crystals of a pair of optical isomers.

C. Manner of operation:
   (a) Batch operation.
   (b) Continuous operation.

In the heretofore proposed batch-type re-

[*Price 5s. 0d. (25p)*]

1,197,809

PATENT SPECIFICATION 1,197,809

DRAWINGS ATTACHED.

Date of Application (No. 32179/68) and filing Complete Specification: 5 July, 1968.

Application made in Japan (No. 9011) on 13 Feb., 1968.

Complete Specification Published: 8 July, 1970.

Index at acceptance:—B1 GX; C2 C(2D19, 3A7V4A1, 3A7V4F1, 3A7V4F2, 3A7V4H, 20Y, 213, 215, 22Y, 220, 227, 246, 247, 25Y, 250, 251, 29Y, 29X, 30Y, 302, 31Y, 313, 32Y, 321, 332, 339, 34Y, 342, 351, 352, 36Y, 360, 361, 362, 366, 367, 571, 581, 591, 601, 62X, 620, 623, 628, 638, 652, 658, 670, 761, 762, 174—198—272, 181—198—280, KK, KN, KR, LK, LR).

International Classification:—B 01 d 9/02.

COMPLETE SPECIFICATION.

Method for Continuous Optical Resolution of Organic Racemates.

We, THE NOGUCHI INSTITUTE, a corporation organised under the Laws of Japan, of 8—1, Kaga-1-chome, Itabashi-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method for continuous optical resolution of a solution of an organic racemate into crystals of desired optical isomer.

Various methods for optical resolution of organic racemates have been heretofore proposed. Methods based on fractional crystallization using a physico-chemical means have been regarded as more advantageous than chemical or biological methods, for the former methods require no expensive reagent for resolution and can be carried out economically on an industrial scale.

A number of methods for optical resolution of organic racemates using physico-chemical resolution have been patented, but these methods have been all based merely on experiments and not on a theory or generalization derived from the experiments. Thus:

(1) The relation between the applicability of resolution methods based on the fractional crystallization and the constitution of organic racemates is not clearly predictable and must apparently be checked experimentally case by case [Chem. Rev. *3*, 297 (1963)].

(2) A basis for controlling the optical resolution utilizing fractional crystallization is not clearly predictable. When the degree of supersaturation of organic racemate is high, the resolution cannot, in general, be carried out successfully. In fact, it has been recommended that the resolution should be carried out below a certain limit. However, such limit is not clearly predictable because the basis of such a limit has not been elucidated. Therefore, such a limit for an individual organic racemate must apparently be experimentally determined case by case.

(3) A large number of resolution means for various organic substances based on fractional crystallization have been proposed. However, what type of means is to be employed depends entirely upon experiment for the case concerned because the resolution is greatly influenced by the physical properties of the organic racemate to be resolved. The heretofore proposed means are as follows:

A. Utilization of supersaturation:
   (a) A means based on the preparation of a supersaturated solution of the organic racemate in advance and successive seeding of crystals of the desired optical isomer.
   (b) A means based on the supersaturation of an organic racemate solution after seeding.

B. Utilization of seeding:
   (a) A means based on seeding crystals of the desired optical isomer.
   (b) A means based on the simultaneous seeding of crystals of a pair of optical isomers.

C. Manner of operation:
   (a) Batch operation.
   (b) Continuous operation.

In the heretofore proposed batch-type re-

[*Price 5s. 0d. (25p)*]

solution crystallization method, full growth of the crystals of the desired optical isomer up to a maximum resolution point and effective recovery of the grown crystals cannot be attained effectively, and when the batch-type resolution is to be carried out on a large scale a large amount of supersaturated solution must be prepared in advance and stored. The solution must be well stirred so that the seeded crystals of the desired optical isomer are uniformly suspended therein, and the temperature and other resolution conditions must be accurately controlled. Further, the grown crystals must be instantaneously separated from the mother liquor at an optimum time. Furthermore, as the resolution proceeds in the solution, the undesired optical isomer tends to crystallize out simultaneously if there is even a slight change in the resolution conditions, and thus there is always a danger that the desired resolution will not be attained.

Continuous resolution methods using a column-type or vessel-type resolution system have been proposed and practiced. However, in all these methods the characteristics of the batch-type resolution have not been incorporated. For example, in the vessel-type resolution system, the deposited crystals increase in amount with time and consequently it is very difficult to carry out the resolution, keeping the system in a stationary state. In these methods, there is always a danger of crystallization of undesired isomer, and once the crystallization of undesired isomer takes place, the desired, already crystallized isomers are contaminated with the crystals of undesired isomers. Thus, in these methods it is necessary to keep the degree of supersaturation low and recycle the solution before the amount of resolved crystals reaches a maximum. Consequently the efficiency is inevitably low.

It is an object of the present invention to provide a method for truly continuous resolution, which can be economically and efficiently carried out on an industrial scale in a readily controllable and stable manner.

According to the present invention a method for continuous optical resolution of an organic racemate comprises forming a suspension of not more than 50% by weight, based on the racemate, of crystals of the desired optical isomer, that is, either L-form or D-form optical isomer, in a supersaturated solution of the racemate having a value α as hereinafter defined of not greater than 2.2 and of not more than 160% supersaturation, continuously moving the solution and suspended crystals together in the same direction through a resolution tube, retaining the suspension in the resolution tube for a shorter time than that at which the percentage resolution starts to decrease in a purity/time resolution curve obtained in a batch-type resolution under the same conditions thereby to allow the suspended crystals to grow, and then separating the thus grown crystal of the desired optical isomer from the mother liquor.

The value α is the ratio of the solubility of the organic racemate to that of the undesired optically active isomer; in other words, the negative of the tangent of the slope of the curve obtained by plotting the amount of racemate as ordinate against the amount of undesired optical isomer as abscissa during a process of resolution as described later with reference to Figure 4.

The invention will now be described in more detail with reference to the accompanying drawings, in which:—

Figures 1 (a) and 2 (a) are diagrams showing the amount of a desired optical isomer deposited from a supersaturated solution of organic racemate with time;

Figures 1 (b) and 2 (b) are the diagrams showing the change in optical purity of the deposited crystals of the desired optical isomer shown in Figures 1 (a) and 2 (a), with time;

Figure 3 illustrates the case when seeding with crystals of a desired optical isomer is ideally carried out in a supersaturated solution of an organic racemate;

Figure 4 is a diagram showing the change in composition of the solution when the resolution proceeds according to Figure 3;

Figure 5 is a schematic view of an apparatus wherein the present method is carried out; and

Figures 6 to 9 are schematic views of various modifications of the apparatus shown in Figure 5.

The present invention is based on the following findings. Optical resolution can be carried out utilizing fractional crystallization under the conditions in which crystals of organic racemate can be crystallized out. As a result of studying the resolution process under the conditions in which crystals of organic racemate mixture can be crystallized out, the present inventors have found that in a batch-type resolution based on adding seed crystals of the desired optical isomer, that is, either L-form or D-form isomer, to a supersaturated solution of organic racemate and allowing the seed crystals to grow, two quite different types of result can be obtained, referred to below as Case A and Case B.

Case A: When the seed crystals of the desired optical isomer, for example, the L-form optical isomer, are added to the supersaturated solution and allowed to grow, the antipode isomer, that is, the D-form optical isomer, crystallizes out simultaneously while the L-form optical isomer is depositing on the seeded crystals. When the amount of desired L-form optical isomer in the de-

posited crystals is plotted against time, a curve having a maximum value, as shown in Figure 1 (a), is obtained. The optical purity of the deposited crystals decreases with time as shown in Figure 1 (b).

Case B: When the seed crystals of the desired optical isomer, for example, the L-form optical isomer, are added to the supersaturated solution and allowed to grow, the antipode isomer, that is, the D-form optical isomer, does not crystallise out appreciably until the L-form optical isomer has been completely deposited on the seeded crystals. When the amount of the desired L-form optical isomer in the deposited crystals is plotted against time, a curve having a maximum value as shown in Figure 2 (a) is obtained. Though the curve is similar to that of Case A, the optical purity of the deposited crystal is maintained at a high level until the D-form optical isomer starts to deposit, as shown in Figure 2 (b). In this respect, Case B is quite different from Case A.

The present inventors found that the difference between Case A and Case B is dependent on the degree of supersaturation of the organic racemate and on the solubility ratio α of the organic racemate to the undesired optical isomer under the resolution conditions.

Further investigation into the cause of the difference between Case A and Case B, particularly as to the degree of supersaturation of the solution of the organic racemate being below a certain limit, revealed that the difference between Case A and Case B depends upon the stability of the resolution mother liquour; that is, upon whether or not the antipode isomer in the mother liquor can be stably held therein for a definite period of time without any crystallization of the antipode isomer. Further, it was found that whether or not the antipode isomer can be stably maintained in the mother liquor depends upon the physical properties of the organic racemate and its component optical isomers under the resolution conditions. More particularly, it was found that whether Case A or Case B occurs depends upon whether or not the ratio of the solubility of the organic racemate to that of the undesired isomer is not greater than 2.2.

In Figure 3, the change in the solid-liquid composition is diagrammatically shown when seed crystals of the L-form optical isomer are added to the supersaturated solution and the resolution ideally proceeds as in Case B. The amount of crystals deposited from the supersaturated solution in the crystallization process is shown by hatching in Figure 3 in comparison with the amount of supersaturated solution above the dotted line. The area below the dotted line shows the amount of saturated solution.

In Figure 4, the change of the composition of the mother liquor as shown in Figure 3 is indicated by plotting amounts in the mother liquor of organic racemate on the ordinate and amounts in the mother liquor of undesired optical isomer, i.e. the D-form optical isomer, on the abscissa. The composition of racemate and D-form isomer in the mother liquor change along the line $y \rightarrow x_0$ when the resolution ideally proceeds as shown in Figure 3. In that case, the ratio of the amount of racemate to the amount of optical isomer, y/x_0 is 2.

As explained above, the line $y—x_0$ of Figure 4 shows the composition when the resolution proceeds ideally; the line $y \rightarrow x_1$ ($y/x_1 < 2$) shows an equilibrium state of the heterogeneous three-component system consisting of organic racemate, undesired optical isomer and solvent in the case of the organic racemate B ($\alpha > 2$); and the line $y \rightarrow x_2$ ($y/x_2 <$) shows an equilibrium state of the heterogeneous three component system consisting of organic racemate, undesired optical isomer and solvent in the case of the organic racemate C ($\alpha < 2$).

At the composition point A of the resolution mother liquor in Figure 4, the amount of D-form isomer accumulated in the mother liquor is x_A. Whether or not x_A can be stably held in the racemate A is explained below. In the case of organic racemate B, an amount x_B of D-form optical isomer is stably held by the supersaturated solution of racemate of amount y_A. In the case of organic racemate C, the supersaturated solution of racemate in an amount of y_A can stably hold an amount x_C of the D-form isomer.

In the case of the racemate B, the difference, $x_A - x_B$, becomes larger during the course of the resolution and much more D-form isomer tends to crystallize out. The optical purity of the deposited crystals with time follows the course as shown in Figure 1 (b). On the other hand, in case of the racemate C, the difference, $x_C - x_A$, becomes larger during the course of the resolution and the amount x_A of the D-form isomer accumulated is stably held in the supersaturated solution. The optical purity of the deposited crystals with time follows the course as shown in Figure 2(b).

The ratio of the solubility α is larger than 2 in the case of the racemate B, and less than 2 in the case of the racemate C. The value α in the case of the racemate A along the line $y—x_0$ is equal to 2.

In other words, the resolution proceeds along the line $y \rightarrow x_0$ when $\alpha = 2$, but when the value α is considerably larger than 2, the D-form isomer tends to crystallize out and thus satisfactory resolution cannot be expected. Only when the value α is equal

to or less than 2 can the resolution be attained as in Case B.

The present inventors have confirmed by experiment that the resolution can be satisfactorily attained in practice without any significant deposition of the D-form isomer if the value α is not greater than 2.2. It seems that, even if the value α is about 2.2, the difference, $x_a - x_b$, is so small that the potential for nucleation is very low, though there is a tendency to start the crystallization of the D-form isomer.

It has been found in practice that, in the case $\alpha \leqq 2.2$, the desired optical isomer alone can be stably grown and crystals of the desired optical isomer having a very high purity can be obtained by the resolution.

Furthermore, it has been found that, in the case of $\alpha \leqq 2$, satisfactory resolution can proceed at a degree of supersaturation of the solution of about 105 to 160%, but in the case of $\alpha = 2.2$ a very high degree of resolution may in some cases be obtainable only at a somewhat lower degree of supersaturation, that is, at up to 140%.

The ratio of solubility of the organic racemate to that of the undesired isomer, α, depends upon the substance to be resolved, the temperature and the solvent.

In order to shorten the deposition time of the desired optical isomer, it is effective to increase the amount of seed crystals.

The amount of seed crystals of the desired isomer to be added must be determined so that the crystallization of the desired optical isomer is completed before the undesired antipode isomer starts to crystallize out in the mother liquor at a given degree of supersaturation. An increase in the amount of seed crystals helps to shorten the crystallization time of the desired isomer and is effective in providing a time allowance to the process sequence before the undesired antipode isomer starts to crystallize out. According to the present invention not more than 50% of the desired optical isomer is added to the solution on the basis of the organic racemate in the solution.

The supersaturated solution containing the seed crystals can be prepared by adding the seed crystals to the supersaturated solution, or by supersaturating the solution after seeding, or by adding the seed crystals to a slightly supersaturated solution followed by further supersaturating the seeded solution.

According to the present invention, optical resolution is carried out continuously on the basis of the study of a batch-type resolution. Thus, the present method for continuous optical resolution of organic racemates can be summarized as follows:

(1) A batch-type resolution of organic racemate is conducted under such conditions that the ratio of solubility α is not more than 2.2; the degree of supersaturation of racemate in the solution is not more than 160%, and the amount of seed crystals is not more than 50% on the basis of the organic racemate in the solution.

(2) The time required for obtaining the maximum percentage resolution is determined.

(3) A suspension of crystals of the desired optical isomer in a supersaturated solution of racemate is formed under the same conditions as those for the batch-type resolution as set forth in item (1) and the thus suspended solution crystals and racemate solution are passed together through a resolution tube in the same direction in a state where no substantial back flow mixing takes place, for a shorter residence time than the time required for obtaining the maximum percentage resolution as set forth in item (2), whereby the suspended crystals grow.

(4) The thus grown seed crystals are separated from the mother liquor.

The method of the present invention will now be described in more detail. A suspension of crystals of the desired optical isomer in a supersaturated solution of organic racemate is formed and both mother liquor and added crystals are allowed to pass through a resolution tube in the same direction in a state where no substantial back flow mixing takes place, to allow the crystals to grow. If the suspension is allowed to flow as what is herein termed "piston flow", i.e. with no substantial back flow mixing, the time t required for the maximum percentage resolution as determined by the batch-type resolution can be accurately attained. That is, by using a resolution tube, the time required for the maximum percentage resolution can be represented by the following formula, $t = V/F$, wherein V stands for the volume of the resolution tube and F stands for the flow rate. In case of piston flow, the time t can be attained by suitably selecting the length of the resolution tube or by controlling the flow rate.

In the case of piston flow, the time t can be fixed directly by the length of the resolution tube. Further, an optimum residence time can be fixed simply by controlling the flow rate, and thus the solid-liquid separation can be carried out immediately at an optimum residence time for maximum percentage resolution.

The grown crystals can be immediately separated before the antipode isomer in the mother liquor starts to crystallize out, even if the degree of supersaturation is high, and thus the crystals of the desired optical isomer having a high optical purity can be obtained in a high efficiency in a short period of time. As explained above the resolution may be carried out in a piston flow, and thus even if the undesired antipode isomer casually

starts to crystallize out during the resolution process, the optical purity of the deposited crystals is partially lowered only in the relevant portion of the piston flow without affecting the rest of the flow.

The present invention is effectively applicable, for example, to the resolution of such organic racemates as amino acids, their derivatives and salts, tartrates, malic acid, chloramphenicol and α-aminocaprolactam hydrohalide.

The optical resolution of threonine described by way of illustraton. 25 g of DL-threonine was dissolved in 100 g of water at 40°C and the resulting solution was cooled down to 15°C. Then, 1 g of L-threonine crystals were added thereto, and the solution was stirred. Supernatant liquor was sampled at predetermined time intervals after the start of stirring and the progress of resolution was determined by measuring the concentration and optical rotation of the sample.

The results are given below:

Time (min.)	Percentage Resolution
10	40%
20	67%
30	80%
40	60%
50	41%
60	20%

$$\text{Percentage resolution} = \frac{\text{D-form isomer in mother liquor (g)/water (100g)}}{\frac{1}{2}[\text{25g (initial concentration)-18g (15°C saturation)}]} \times 100$$

It is seen from the foregoing that the maximum percentage resolution is between 20 and 30 minutes.

Another example of the optical resolution is as follows. 5 g of DL asparagine monohydrate was dissolved in 25 g of water at 40°C and the resulting solution was cooled down to 35°C. Then, 0.5 g of D-asparagine crystals were added thereto as seed, and after 23 minutes the solution was subjected to solid-liquid separation, whereby 1.21 g of crystals was obtained. The optical purity was found to be 99.8% by measuring its optical rotation. After 35 minutes, the solution was subjected to solid-liquid separation under the same conditions, whereby 1.4 g of crystal was obtained. The optical purity was 89%. It is seen from the foregoing results that the time for the maximum resolution is between 20 and 30 minutes in case of threonine and between 25 and 35 minutes in case of asparagine.

In the present continuous resolution method, the grown crystals are to be separated from the mother liquor not later than the time of the maximum percentage resolution under the given temperature, concentration and other conditions.

In order to form the suspension of crystals of the desired optical isomer in a solution of racemate, the crystals of the desired optical isomer may be added in a dry state, or in a suspended state where the crystals are suspended in a saturated or unsaturated solution of racemate mixture or, in a liquid state if the nucleation of added optical isomer preferentially takes place even in the solution supersaturated with racemate.

It is very simple to maintain the entire resolution tube at a constant temperature. Alternatively a suitable temperature gradient may be given to the resolution zone.

Some forms of apparatus wherein the present method may be carried out will now be described.

In Figure 5, a solution of racemate is fed from a tank 1 through a valve or pump 2 to a cooler 3, wherein the solution of racemate is cooled and brought into a supersaturated state. The supersaturated solution of racemate formed in this section then reaches a junction 4. At the same time the desired optical isomer is supplied from a tank 5 to the junction 4 through a valve or pump 6, and mixed with the supersaturated solution of racemate mixture, whereby a suspension of the desired optical isomer in the supersaturated solution is obtained. As the suspension passes through a coiled resolution tube 7 having a water-cooled jacket under such conditions that no substantial back flow mixing takes place, the crystals of the desired optical isomer are allowed to grow. The grown crystals are separated from the mother liquor in a solid-liquid separator 8 connected to the outlet end of the tube 7

In Figure 5, the supersaturated solution of racemate mixture is prepared by cooling the solution in the cooler 3, but the supersaturation can be attained not only by a cooling means, but also by neutralization, concentration, addition of a water-miscible organic solvent to the aqueous solution of racemate, pH adjustment or other means. In order to obtain a desirable degree of supersaturation, the tube 7 may have a suitable temperature gradient.

The junction 4 of Figure 5, where the supersaturated solution of racemate and the crystals of the desired optical isomer are mixed together to suspend the latter in

the former, may be provided with a stirring means 9 for improving the mixing of the supersaturated solution from the tank 3 and the optical isomer from the tank 5, as shown in Figure 6. Furthermore, the optical isomer may be continuously injected from the tank 5 into a stream of the supersaturated solution of racemic mixture from the tank 3, as shown in Figure 7.

Instead of the helical tube 7 as shown in Figure 5, a straight tube as shown in Figure 8, or a sinuous tube as shown in Figure 9, or other shaped tube may be employed. It is desirable to control the resolution temperature from the outside of the tube to remove the heat of crystallization and maintain a proper degree of supersaturation in the resolution tube. Furthermore, a straight resolution tube may be provided with an internal course pitch screw stirrer, as shown in Figure 10, to conduct stirring gently so that no substantial back flow mixing takes place.

Further, it is desirable that at least two solid-liquid separators 8 are provided in parallel so that prompt solid-liquid separation of the slurry discharge from the spiral passage 7 can be conducted continuously by switching one to another.

The crystals of optical isomer to be introduced from the tank 5 and mixed with the organic racemate at the junction 4 in Figure 5 may be in a dry state, or in suspension in a solution of the same form of optical isomer or in a saturated or unsaturated solution of the racemate.

Stirring may be carried out at the junction 4 to suspend the crystals of optical isomer in the supersaturated solution of racemate, if necessary.

Further, the system for adding the optical isomer can be omitted in the case where a saturated solution of a racemate (such as threonine or valine hydrochloride) has no more ability to dissolve the optical isomer. In this case the solution of racemate is cooled down by the cooler (3) to crystallize out only the desired optical isomer and the growth of crystallized optical isomer is carried out in the resolution tube 7 having a temperature gradient. In such a case the apparatus is simpler.

Further, in the case where only a desired optical isomer is preferentially nucleated from a supersaturated solution of both racemate and optical isomer, the optical isomer can be added in solution form to the supersaturated solution of racemate at the junction 4.

In moving the suspension it may be subjected to stirring in a direction at an angle to the flow direction in such a manner that the crystals can contact supersaturated solution of racemate and smoothly grow without substantial back flow mixing.

To recover the antipode isomer remaining in the resolved mother liquor, the conventional method may be employed as well as the present method. The crystals of racemate mixture may be added to the resolved mother liquor to dissolve seleotively only the optical isomer in the antipode form with respect to the optical isomer remaining in the mother-liquor, and the thus obtained slurry may be applied as feed solution to further resolution according to the invention.

Furthermore, the present method can be carried out individually in resolution tubes specific for L-form isomer and D-form isomer provided in parallel, or in series.

The apparatus for carrying out the present method may be very simple in structure and the temperature control is also simple, so that the resolution can proceed at the temperature most favourable to it.

The following Examples illustrate the invention.

EXAMPLE 1

A solution of DL-threonine having a concentration of 25g of DL-threonine in 100 g of water was placed in a vessel over a water bath kept at 40°C and fed to a cooling tube at a rate of 400 ml/min. The solution cooled down to 15°C, providing 147% supersaturation, and was fed to a resolution tube. A suspension containing one part of pulverized L-threonine suspended in two parts of saturated aqueous solutions of L-threonine at 15°C was added to the solution at the junction through a means as shown in Figure 7 at a rate of 50 ml/min.

The resolution tube was a straight one having an internal diameter of 40 mm and a length of 80 cm and was placed in a horizontal position. A helical glass stirrer having a diameter of 35 mm was inserted in the resolution tube and slowly rotated at 80 rpm. An opening was provided at the upper side of one end of the resolution tube and another opening was provided at the under side of other end of the resolution tube. A jacket was provided outside the tube and water at 15°C was circulated through the jacket.

Fifteen such horizontal tubes were employed, the tubes being connected in series.

The slurry discharged from the resolution tube was centrifugally separated in a continuous manner. The operation was continued for three hours, and the deposited crystals were obtained at a rate of 12 g/min. on average, and the optical rotation was −28° (about 1% at 20°C). The value of α was 1.93.

EXAMPLE 2

The same apparatus as in Example 1 was employed.

A solution containing 20 g of DL-aspara-

gine monohydrate dissolved in 100 g of water and kept at 55°C was fed to the resolution tube at a rate of 400 ml/min. On the other hand, 2 kg of L-asparagine was suspended in 4 kg of saturated solution of DL-asparagine at 33°C, placed in a vessel over a water bath kept at 35°C, and stirred so that the crystals remained suspended (supersaturation: 147%). The thus prepared slurry was fed to the resolution tube at a rate of 40 ml/min. The operation was continued for 2 hours, and the deposited crystals were obtained at a rate of 18.7 g/min. on average. The optical purity of the crystals was 96.6%, and the value of α was 1.95.

EXAMPLE 3

A saturated aqueous solution of the ammonium salt of DL-acetyltryptophane at 80°C was fed to the apparatus as shown in Figure 5 at a rate of 100 ml/min. and cooled down to 65°C in the cooler, providing 148% supersaturation, whereas dry crystals of the ammonium salt of D-acetyltryptophane having a particle size of 200 mesh and under were fed to the apparatus at a rate of 4 g/min. The resolution was conducted in a coiled tube having an internal diameter of 6 mm and a length of 15 m, warm water at 65°C being circulated around the outside of the tube.

The discharged slurry was successively filtered through a heated glass filter, and the filtered crystals were washed with a small amount of acetone. At one hour after the start of operation, the crystals were sampled for 10 minutes. The amount of sampled crystals was 98 g and the optical purity of the crystals was 98.3%. The value of α was 1.66.

EXAMPLE 4

A saturated solution of DL-acetylglutamic acid at 60°C was fed to a resolution apparatus at a rate of 100 ml/min., and cooled down to 49°C in the cooler, providing 137% supersaturation. On the other hand, a suspension of one part of L-acetylglutamic acid having a particle size of 200 mesh and under in three parts of saturated aqueous solution of DL-glutamic acid at 45°C was fed to the solution at a rate of 30 ml/min. Two resolution tubes having an internal diameter of 6 mm and a length of 15 m were employed. Water at 47°C was circulated around the outside of the first tube and water at 40°C around the outside of the second tube. The discharged slurry was separated in a heated centrifuge. At 80 minutes after the start of operation, crystals were sampled for 10 minutes. The amount of sampled crystals was 118 g, and the optical purity was 97%. At 150 minutes after the start of operation, the crystals were sampled for 10 minutes, the amount of sampled crystals was 103 g and the optical purity was 95.8%. The value of α was 2.14.

EXAMPLE 5

A solution of homocysteic acid consisting of 50 g of racemate mixture and 7.5 g of L-form optical isomer per 100 g of water was kept at 60°C, and fed to a resolution apparatus at a rate of 200 ml/min. by a pump. The solution was cooled down to 50°C by a cooler, providing 120% supersaturation. The solution was vigorously stirred at the inlet of the resolution tube to crystallize out nucleus crystals. Two coiled tubes having an internal diameter of 10 mm and a length of 13 m were used, water at 43°C being circulated in a jacket of one tube and water at 35°C being circulated in a jacket of the other tube. Operation was continued for 45 minutes. The crystals were obtained at a rate of 23.2 g/min. and the optical rotation was 21.8. The value of α was 1.48.

EXAMPLE 6

An aqueous solution of monoammonium monosodium DL-tartrate tetrahydrate (concentration of racemate: 50.22% by weight including the water of crystallization; concentration of L-form isomer: 2.16%) was placed in a tank kept at 30°C and passed through a cooling tube and resolution tube controlled to 13°C, by a constant feed pump. The cooling tube was a coiled glass tube having an internal diameter of 0.5 mm and a length of 7.8 m, the coil diameter being 4.5 cm. The solution was cooled to the desired resolution temperature of 13°C by passing the same through the cooling tube. The cooled solution was of 134% supersaturation. The resolution tube connected to the cooling tube consisted of a nucleation part and a resolution part. The nucleation part was in the form of a straight tube having an internal diameter of 22 mm and a length of 41 cm, and was placed horizontal and provided along the axis of the tube with a stirrer rotating at 700 rpm. The resolution part was in the form of a coiled glass tube having an internal diameter of 10 mm and a length of 6.5 m, the coil diameter being 7 cm. After a residence time of 4.2 minutes in the resolution part, the slurry discharged from the bottom end of the resolution part was subjected to centrifugal separation.

WHAT WE CLAIM IS:

1. A method for continuous optical resolution of an organic racemate which comprises forming a suspension of not more than 50% by weight of crystals of the desired optical isomer based on the racemate in a supersaturated solution of the racemate having a value α as hereinbefore defined of

not greater than 2.2 and and not more than 160% supersaturaion continuously moving the solution and suspended crystals together in the same direction through a resolution tube, retaining the suspension in the resolution tube for a time shorter than that at which the percentage resolution starts to decrease in a purity/time resolution curve obtained in a batch-type resolution under the same conditions thereby to allow the suspended crystals to grow, and then separating the thus grown crystals of the desired optical isomer from the mother liquor.

2. A method according to Claim 1 wherein the crystals of the desired optical isomer are added to the solution in a dry state to form the suspension.

3. A method according to Claim 1 wherein the crystals of the desired optical isomer are added to the solution in a suspended state in a saturated or unsaturated solution of the desired optical isomer or the organic racemate to form the first-mentioned suspension.

4. A method according to Claim 1 wherein a solution of the crystals of the desired optical isomer are added to a solution of the organic racemate with subsequent cooling to effect crystal formation and form the suspension.

5. A method according to Claim 1 wherein the crystals of the desired optical isomer are dissolved in a solution of the organic racemate with subsequent cooling to effect crystal formation and form the suspension.

6. A method according to Claim 1 wherein crystals of organic racemate are added to a previously resolved mother liquor and partially dissolved therein to form the suspension.

7. A method according to any of the preceding claims, wherein the racemate is an amino acid, or derivative or salt thereof, a tartrate, malic acid, chloramphenicol or α-aminocaprolactam hydrohalide.

8. A method for continuous optical resolution of an organic racemate substantially as described in any of the Examples.

9. Optical isomers which have been separated from an organic racemate by a method as claimed in any of the preceding claims.

KILBURN & STRODE,
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon), Ltd.—1970.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY
from which copies may be obtained.

1197809 COMPLETE SPECIFICATION

3 SHEETS This drawing is a reproduction of the Original on a reduced scale

Sheet 1

FIG. 1

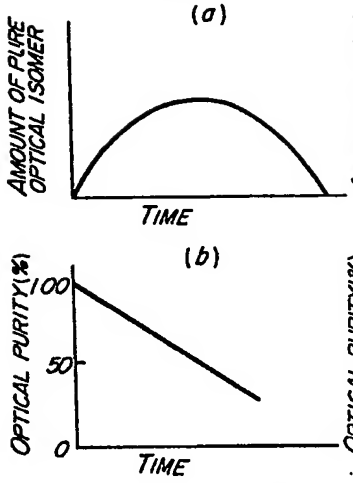


FIG. 2

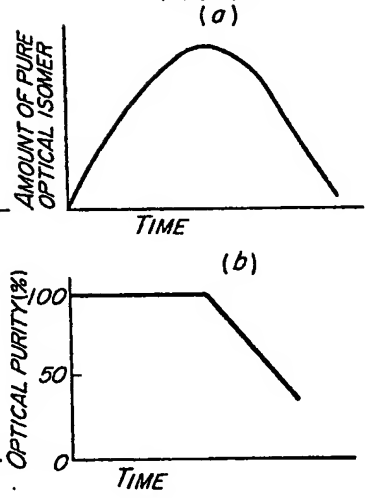


FIG. 3

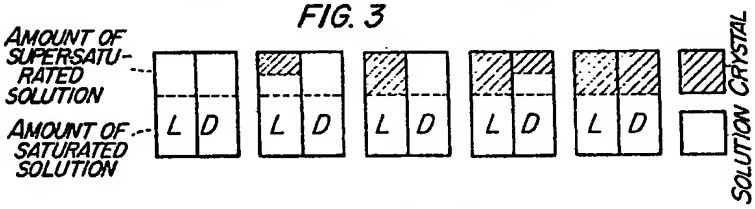
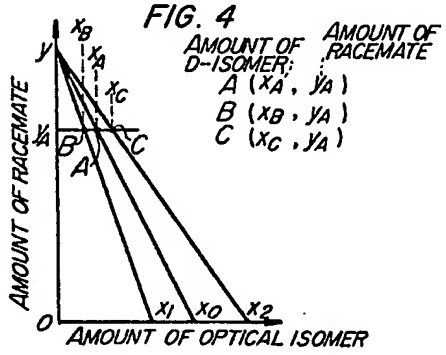


FIG. 4



1197809 COMPLETE SPECIFICATION
3 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 2

FIG. 5

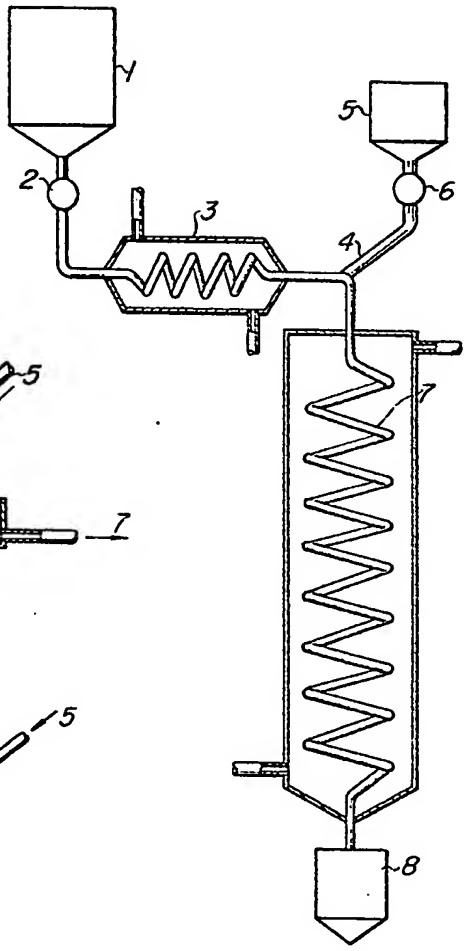


FIG. 6

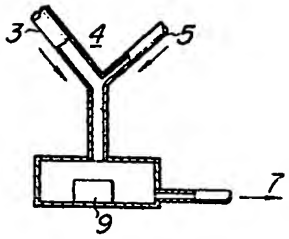
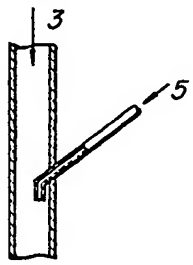


FIG. 7



1197809 COMPLETE SPECIFICATION

3 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 3

FIG. 8

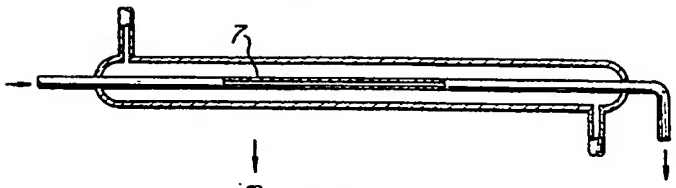


FIG. 9

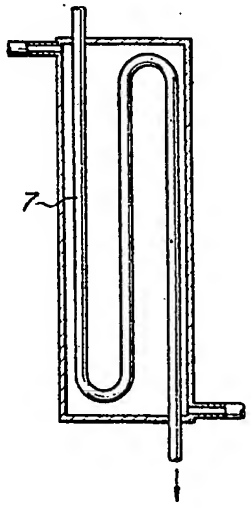


FIG. 10